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Environmental Factors and the Development of Disease and Injury in the Alimentary Tract

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This review examines interactions between the alimentary tract and environmental agents. In these interactions the alimentary tract is considered as an integrated organ system extending from mouth to anus. The alimentary tract shares with the skin and its appendages and the respiratory system the distinction of being a portal of entry into the human body for environmental agents as well as a target for their action. Food and water-borne environmental agents enter the body via the alimentary tract. By injurying the alimentary tract environmental agents alter their portal of entry and thereby modulate their effects on the organism. Such modulation may enhance or depress effects of these agents. Interactions between environmental factors and the alimentary tract depend on (1) factors related to the alimentary tract that are determined by anatomic, physiologic, and biochemical considerations; (2) factors related to the environmental agents; and (3) individually determined factors. The role of these factors in development of disease and injury is considered. Environmental diseases of the alimentary tract and environmental agents acting on the gut are discussed and recommendations are made for future research.

Introduction

This examination of effects of environmental factors on the gastrointestinal tract is limited anatomically to organs comprising the tube extending from mouth to anus. Organs considered include oral cavity, pharynx, esophagus, stomach, small intestine, colon, and rectum. Exclusion of appendages to the alimentary tract such as liver and pancreas allows a unified pathophysiological approach. Essentially all factors and agents acting on the alimentary tract are considered including chemical, physical, and societal factors. Chemical factors include environmental pollutants, and food additives, particularly those with carcinogenic potential (*1*). Physical factors considered include radiation and thermal effects. Societal factors include stress, noise, etc., particularly in relation to peptic ulcer and functional colonic disease (*2*). Characteristics of the subject determining individuality or uniqueness of alimentary tract response to environmental factor are also considered, including habits, use of nonprescription drugs, alcohol, tobacco, presence of systemic disease, etc.

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To focus this analysis, certain environmental factors are excluded from detailed consideration. Thus, nutrients *per se* will not be discussed as environmental factors, although excesses and deficiencies injure the alimentary tract. Likewise, infectious agents such as bacteria, viruses and parasites are not within the scope of this report, although they represent the commonest well categorized factors injurious to the alimentary tract. However, both nutritional status and enteric infections modify responses of the alimentary tract to environmental factors such as chemical and physical agents. Therefore, nutrition and infectious enteritis are considered in the category of modulating factors determining individual responses to environmental agents. Vitamins, minerals, prescription drugs, and drug interactions causing toxicity to the alimentary tract are outside the scope of this report, except as illustrations of mechanisms.

Thus, the primary purpose of this report is to review the important interactions between environmental factors and the alimentary tract. Diseases of the alimentary tract are of major importance as causes for disability and death on a world-wide scale. Environmental factors play a major role, or are intimately involved in pathogenesis of many alimentary tract diseases.

Alimentary Tract as a Portal of Entry System

The gastrointestinal tract has a unique role in relation to environmental factors. This system of organs is the major interface between the individual and the environment. Therefore, injury to the alimentary tract by environmental factors not only damages the organ system itself, but also alters function of the portal of entry for most such factors. In this way factors injurious to the alimentary tract modulate their own toxic effects or effects of other agents on the individual by altering delivery of agents to the organism. The injury response may limit or enhance effects of environmental factors. For example, self-limited diarrheal diseases caused by viral agents or microorganisms such as certain *Salmonella* strains are shortened if left to run their course rather than treated symptomatically by antidiarrheal agents such as Lomotil. The diarrheal fluid secreted in response to enterotoxin or to invasion of the mucosa aids in eliminating the injurious agent. The motility response of the alimentary tract is also more effective in removing toxin if not impaired by treatment with anticholinergic agents. More often, injury enhances effects of other agents. For example, damage to the mucosa by environmental factors such as ethanol (*3*) may impair its barrier function and promote absorption of substances to which it is normally impermeable such as macromolecules (allergenic proteins) or charged molecules (strong acids or bases). In addition, damage to the alimentary tract causes secondary effects on the organ system itself and on other organs. Agents causing malabsorption, such as environmental factors causing tropical sprue, or the gliadin fraction of wheat gluten causing celiac sprue, alter the nutritional state of the entire organism. Nutritional status of the organism and its tissues alters response to environmental toxins (*4*). Tropical sprue, a disease in part environmentally determined, best illustrates secondary effects of intestinal disease on the alimentary tract and the organism. Malabsorption caused by mucosal damage from tropical sprue causes further depletion of nutrients such as folic acid in a population already marginal in nutrition. Folate deficiency causes further damage to the mucosa by limiting cell proliferation necessary for normal replacement. This further depresses absorption, initiating a self-perpetuating cycle.

Interactions between Environmental Factors and the Alimentary Tract

In order to consider the role of environmental factors in causing disease or injury to the alimentary tract, it is essential to develop the setting in which these events occur. This requires development of the relationships of the organ system and its normal function to the environmental factors as well as the role of homeostasis within the system. Alterations in homeostasis produced by environmental factors that lead to disease or injury can best be examined in this setting. An analysis of development of disease and injury to the alimentary tract must also focus on specific organs, their diseases, and mechanisms of processes involved. However, it is essential to begin by considering general principles governing relationships between environmental factors, particularly specific chemical agents, and the alimentary tract.

Although most environmental agents enter the organism through the mouth, inhaled substances are trapped in mucus of the nose and nasopharynx and enter the alimentary tract by being swallowed. For example, inhaled allergens not only enter the pulmonary system, but a large fraction is swallowed and enters the alimentary tract. The ultimate effects of environmental factors on the alimentary tract and on the organism itself depend on effects related to the alimentary tract and effects related to the factor or agent itself.

Effects Related to the Alimentary Tract

The true load of an environmental agent on the alimentary tract and on the organism is determined only in part by the amount entering through the mouth and nasopharynx. Effects of entering load can be greatly altered by factors acting within the alimentary tract and through other organs. Alimentary tract factors may act intraluminally, at the brush border interface between mucosal cell and lumen, intracellularly, as well as within the submucosal tissues. Intraluminally, the agent may be degraded by gastrointestinal tract secretions. Intraluminal processes include chemical reactions such as acid catalyzed hydrolysis in the stomach, or base catalyzed hydrolysis in distal small intestine. Enzymes in gastrointestinal tract secretions, such as proteases, carbohydrases, and lipases may act on agents.

Many agents are relatively insoluble in contents of the gastrointestinal tract. The undissolved portion will be minimally affected by intraluminal factors and may be excreted from the alimentary tract in the feces in the same form it entered, without affecting the organism. The portion of the agent that is in solution is subject to intraluminal attack and is available for absorption as it contacts the brush border of the mucosal cell. A small proportion of undissolved agent may be taken up by pinocytosis. Not all of the agent in solution is absorbed; i.e., enters the body. Polar or charged molecules may be virtually unabsorbed. Highly lipid-soluble substances may be absorbed essentially completely. Physical properties are not the only factor determining absorption. Agents might interact with the glycocalyx of the brush border and simply be adsorbed to this glycoprotein surface. Other agents may be bound intracellularly, e.g., iron binding to ferritin in mucosal cells of small intestine. Both surface and intracellularly bound agents reenter the lumen, when the mucosal cell is exfoliated at the end of its 24–48 hr life span.

Agents that enter the cell through the brush border usually traverse the cell and exit through the basal-lateral cell membrane to pass into the portal circulation or the lymphatic system. Certain agents are metabolized in mucosal cells, e.g. conjugation of estrogens to form glucuronides (*5*). After certain agents such as indomethacin are absorbed and carried in the portal circulation to the liver, they are conjugated with glucuronic acid and excreted into the bile to reenter the intestine. Thus, the load of such an agent on the intestine is amplified by enterohepatic recirculation. Presence of bacteria with β-glucuronidase in the intestine may regenerate the original compound or a metabolite and cause damage to the intestine.

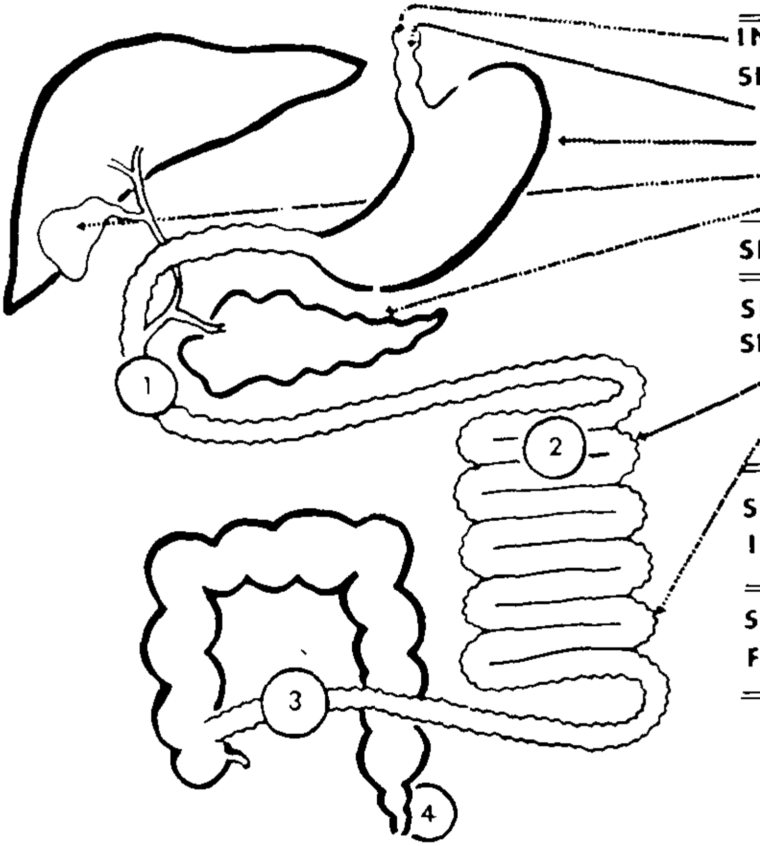
After environmental agents enter the alimentary tract, their effects depend on factors related to the individual exposed and to the agent itself. As discussed below, individual factors include age, sex, disease; agent factors include total dose, rate and pattern of entry, and physical state.

Behavior of Agents within the Lumen of the Alimentary Tract

Behavior of the agent after entry is determined by anatomic and physiologic characteristics within the alimentary tract. The physical dimensions of the luminal milieu within which effects on environmental agents occur is shown in Figure 1, and relationships between normal and disease states are described (*6*). In the stomach, contents are usually in the pH range of 1–3.5, most commonly 1–2.5. Normal motor activity of the stomach causes thorough mixing of agent and gastric contents. Depending upon whether the agent enters the fasting stomach or with a meal, gastric effects on the agent will differ. Many factors influence gastric emptying. Emptying of the fasting stomach is rapid, 30 min or less. After a high-fat meal, several hours may elapse before the stomach empties. Factors related to the contents include type, volume, viscosity, temperature, caloric density, buffering capacity; individual factors include age, health, emotion, activity, posture; extraneous factors include drugs, e.g., anticholinergics.

Delivery of gastric contents to duodenum is followed by an increase in pH to 5–7 as the jejunum is traversed. Enzymes in gastric secretions are the proteolytic enzyme pepsin, active only at low pH, and colipase. The main site of enzymatic activity is the small intestine. Pancreatic enzymes are quantitatively most important and include proteases, carbohydrases and lipases. Intestinal enzymes are also secreted intraluminally. Bile also enters and mixes with duodenal contents. Bile acts primarily through the detergent properties of bile acids, which tend to form mixed micelles with lipophilic molecules. Pancreatic and biliary secretions are alkaline, and pH of intestinal contents gradually increases to 7–8 as they pass into the ileum. The particular characteristics of each site determine the form and behavior of agents at that locus. Stomach has much less absorbing surface than small intestine, the organ with the greatest surface area. Factors determining gastric emptying rate have already been discussed. Rate of transit through proximal small intestine is rapid, measured in minutes for duodenum and hours for ileum. Transit through the colon requires 1–2 days.

Bacterial Ecosystem: The normal alimentary tract contains a bacterial ecosystem integral to its development, growth and function. The alimentary tract is sterile at birth and is colonized by bacteria derived from the environment. Oral contamination is the primary initial source for development of enteric flora, with minor contribution from anal contamination. *Escherichia coli, Clostridium welchi* and streptococci appear first and colonize



24 HOUR DATA

SITE	H_2O ml	Na mmoles
INTAKE	2000	50-150
SECRETIONS: Fed		
SALIVARY	1000	50
GASTRIC	2000	100
BILIARY	1000	200
PANCREATIC	2000	150
SITE 1, Total	8000	600
SITE 2		
SECRETIONS: Fasting		
JEJUNAL	4000	560
ILEAL	2200	280
SITE 3 ILEOCECAL FLOW: Fed	1500	200
SITE 4 FECAL EXCRETION	100-200	5

FIGURE 1. Water and electrolyte content of the alimentary tract during a 24-hr period. Assuming no net absorption prior to arrival at site 1 (duodenum), the sum of volumes of intake and secretions is 8 liters. Total sodium arriving at this site is 600 mmole. Because of high water permeability of the duodenum, the solution is isotonic. Rate of small intestinal secretion measured as flow rate of fasting intestinal contents is 2.5-3.0 ml/min in proximal jejunum (site 2) and 1–2 ml/min in ileum. It was measured by positioning a tube with a proximal inflow and a distal sampling site in the intestine. An isotonic solution containing a nonabsorbed "marker" polymer (polyethylene glycol) was infused at a known constate rate through the inflow opening and collected at the distal sampling site. For example, if marker concentration is diluted to half its initial value, then secretions must be entering the perfused segment at the same rate as the infusion. At an infusion rate of 1 ml/min total flow rate in the segment is 2 ml/min, and half of this is endogenous secretions. When measured in the fasting individual, this is flow rate of fasting intestinal contents, assuming that the technique for measurement does not perturb the system. Flow across the ileocecal valve (site 3) measured over a 24-hr period (the sum of both the slower rates during fasting and more rapid flow after feeding) is only 1500 ml. Therefore, most of the input of sodium and water is absorbed in the distal small intestine, but sodium and water conservation is the function of the colon. From Schedl (6). Reproduced through the courtesy of the W. B. Saunders Co., Philadelphia, Pa.

within a few hours of birth. Anaerobic lactobacilli and enterococci become established at 24 hr and increase for 10-21 days while coliforms are decreasing. Bacteroides species, which will become the dominant colonic organisms, appear at 10 days and rapidly increase in concentration. By 3–4 weeks after birth, the characteristic flora of the adult is well established.

Normally the stomach and proximal small intestine contain relatively few bacteria. The jejunum is free of organisms in one-third of normal subjects or contains 10^1–10^4 organisms per gram of contents. Organisms present are gram-positive aerobes and facultative anaerobes such as lactobacilli and enterococci. Coliforms are present only transiently and rarely exceed 10^3 per gram. The normal ileum harbors the same flora in one-third of healthy subjects. In two-thirds of subjects concentrations of organisms are increased to 10^5–10^8 organisms per gram and includes coliforms and bacteroides, which are not indigenous to the jejunum.

The concentration of microorganisms increases enormously distal to the ileocecal valve to 10^9–10^{11} per gram colonic contents or feces. Despite the difficulties in culturing them, fastidious anaerobes outnumber aerobes and facultative anaerobes 10,000 to 1. Bacteroides, anaerobic lactobacilli, and clostridia are the major groups. It is to be understood that species variations in anaerobic bacterial flora are considerable and that the taxonomy of anaerobes is more complex than indicated by the term bacteroides. Normal flora bacteria are present in luminal contents, adhere to the surface of the bowel wall, and are found in the fuzzy coat, but do not penetrate microvilli.

Enteric flora in an individual remain stable over prolonged periods. In the proximal alimentary tract, the site of digestion and absorption of most nutrients, host mechanisms limit bacterial proliferation and present overgrowth. The normal bacterial ecosystem is the result of the balance between factors producing contamination and "cleansing" factors. The most important cleansing factor in the small intestine is normal gastrointestinal motility, which propels contents through the alimentary tract. The presence of the normal bacterial ecosystem resists and prevent colonization by extraneous organisms, and gastric secretions, particularly hydrochloric acid, and bile, have antibacterial properties. This ecosystem has the potential to interact with all environmental factors entering the alimentary tract. Such interactions might alter the environmental factor or the bacterial ecosystem itself. Individual factors must also be considered in relation to the bacterial ecosystem. Some patients have bacterial overgrowth in the small intestine with proliferation of bacteria to numbers normally found only in the colon. This overgrowth would be expected to greatly exaggerate bacterial ecosystem-related interactions with environmental factors. In individuals with intestinal overgrowth, interactions would occur in the small intestine amplifying an effect ordinarily occurring primarily in the colon. If the interaction promoted intestinal absorption of the agent, absorption would be greatly increased, since the small intestine is normally the major site for absorption.

The following conditions are associated with proliferation of normal bacteria abnormally in the small bowel lumen: (1) impaired motility due to systemic sclerosis involving the small intestine, degeneration of myenteric plexuses, autonomic neuropathy due to diseases such as diabetes; (2) altered anatomy producing small intestinal strictures with proximal stasis or blind loops causing stasis of intestinal contents in conditions such as afferent loop following gastrectomy, or diverticula; (3) achlorhydria as a result of gastric surgery or gastric atrophy as in pernicious anemia. Other diseases also associated with abnormal flora of the small intestine include liver disease, tropical sprue and celiac sprue.

Organisms of the alimentary tract alter chemical substances present in the lumen (*7*). This has been most extensively studied for fecal organisms, but also occurs in the small intestine, particularly in conditions of bacterial overgrowth with fecal organisms. Chemical reactions occurring in the small intestine are potentially of greater importance. If the reaction product were more toxic and more readily absorbed, effects on the host would be amplified. Conversely, if reaction products were less toxic and more poorly absorbed, the protective effect would be enhanced. The small intestine and the host would be protected. The following general effects of the bacterial ecosystem should be considered: conversion of drugs, food additives and food substances to toxic products or carcinogens; conversion of inert environmental agents to toxic forms; prolonging the action of environmental agent by promoting enterohepatic recirculation; synthesis of toxic products, e.g., ammonia from hydrolysis of urea by bacterial urease, as well as other toxic substances from protein. Effects of such agents are most pronounced in patients with liver disease who are susceptible to encephalopathy from such agents.

Pertinent information on some of these effects is already available. Many substances, including ingested environmental factors as well as those entering through other portals, are excreted in the bile as conjugates, particularly glucuronides. Glucuronides are highly polar molecules and are not absorbed. If hydrolyzed by bacterial β-glucuronidase at an intestinal level where they can be reabsorbed, an enterohepatic circulation of the deconjugated agent is established. This prolongs the action of an agent and thereby enhances toxicity. The hypnotic glutethimide, the fungicide griseofulvin, the antibiotic chloramphenicol, and the antiinflammatory agent indomethacin are probably handled in this way.

Intestinal ulcerations from indomethacin can result from this amplification of dose. Thus, the cumulative biliary excretion of indomethacin and its conjugates has been determined for 5 laboratory species and man (*8*). The wide range of this amplification is 30-fold, from 13% of dose in rabbit to 362% of dose in dog. This provides a quantitative correlate to the wide species variation in sensitivity to indomethacin related lesions. Extrapolation to man predicts a therapeutic ratio of about 20:1 with respect to intestinal irritation. This amplification of toxicity can be prevented or attenuated by specific chemicals such as D-glucaro-1,4-lactone (*9*), an inhibitor of bacterial and intestinal β-glucuronidase. This agent shortened effects of phenobarbital and progesterone, substances conjugated to glucuronic acid. It is possible that agents having similar effects are ingested. Certain plant glycosides including cascara, senna, and cardiac glycosides are probably changed into active derivatives by intestinal flora, since the parent compounds are relatively inert in germ-free animals. Certain products formed from glycosides, e.g. products from cycasin, may be carcinogenic. Thus, formation of carcinogens from ingested substances may depend on gastrointestinal flora. There is some variability of intestinal flora with diet and this may contribute to differing geographical incidences of gastrointestinal malignancies, such as large bowel cancer. Recent advances in this field have been reviewed (*10, 11*).

Digestive Enzymes: Digestive enzymes are the most potent chemical agents acting within the lumen of the gastrointestinal tract. Therefore, luminal enzymes have great potential for changing behavior of environmental factors. Pancreatic enzymes are of greatest importance in the normal individual. For example, deficiency of pancreatic lipase leads to malabsorption of fat. The resulting increased fecal excretion of fat would promote excretion of environmental factors with lipophilic properties.

Of particular interest with respect to interactions with environmental factors are deconjugating enzymes in pancreatic secretions such as glucuronidases and sulfatases. Carcinogens secreted in bile after conjugation with glucuronic or sulfuric acid are poorly absorbed polar charged molecules. Deconjugation greatly promotes absorption of the carcinogen and its continuing enterohepatic recirculation.

Fiber: Fiber comprises indigestible plant components of the diet. The chemical composition of fiber is largely polysaccharide, and cellulose is a major component. Information currently available does not define effects of presence or absence of fiber on the organism. Fiber itself is assumed to be virtually inert physiologically, and to exert its effects through its physical and physicochemical properties.

It is possible that dietary fiber plays a role with respect to actions of environmental agents. Fiber may interact with ingested chemical agents altering their absorption or entry into the body (*12*). Hence, fiber may play a role in the intraluminal, membrane, brush border, or absorptive stages of the interaction of the alimentary tract with environmental agents. Fiber could be protective against effects of environmental pathogens by adsorbing them, preventing their absorption; by increasing their rate of passage through the alimentary tract, thereby decreasing their absorption. Toxic effects of cyclamate and amaranth (Red Dye No. 2), for example, are controlled by fiber (*13*). Fiber adsorbs bile salts, depressing their normal reabsorption in distal ileum and increasing their fecal excretion.

Too low a level of dietary fiber has been linked with cancer of colon and rectum and diverticular disease of the colon. Presumably, the appropriate amount of fiber in diet would be preventive for these diseases. Excessive amounts of dietary fiber could be deleterious despite its inertness: fiber by its bulk would require that larger amounts of food be eaten to supply nutrients, particularly calories. It is unlikely that the proportion of fiber to nutrient would ever be so great that the resulting volume of food required for meeting caloric needs would be so great that it could not be ingested. Excessive amounts of fiber might also cause depletion of calcium, magnesium, trace metals (*14*), bile salts, etc. Thus, fiber probably shows properties of nearly all environmental agents: damage if present in too small or large an amount, with an optimal intermediate dose.

Role of Mucosal Cell

Cell Membrane Structure and Function: Absorptive Processes The limiting membranes for cells lining the alimentary tract differ in properties for the various organs, but have certain common features. The basic structure is classically described as a double protein–lipid bilayer. A centrally located double lipid layer is the backbone of the membrane. Each lipid layer comprises polar and nonpolar portions. Phospholipids comprise a major component of the lipid fraction of the membranes. Phospholipid molecules are elongated and have a polar end containing phosphate esters and nitrogen bases, and a lipoidal end consisting of long chain fatty acids. The lipoidal membrane backbone comprises a double layer with the polar portions of the phospholipid facing the outer and inner aspect of the cell membrane. The central portion of the backbone contains the lipoidal ends of the phospholipid molecules from both outer and inner faces of the polar ends of the lipid double bilayer. Both outer and inner polar faces are coated with protein.

This membrane behaves as if it were discontinuous and penetrated at intervals by water-filled pores lined by fixed negative charges. Uncharged water-soluble substances of small molecular size, less than 4 Å in diameter, such as urea, are absorbed by simple diffusion through the water filled channels. Most molecules, including environmental agents, are too large to be absorbed through pores and traverse the cell membrane itself. The protein–lipid bilayer serves as solvent for lipoidal molecules during passive transport. In this process the driving force is concentration gradient: the environmental agent moves from a higher concentration in the lumen into the cell membrane, then into the cell, and out of the cell into the blood, where concentration of the agent is maintained at a very low level as it is distributed to the body. The concentration gradient of agent from lumen to organism that permits absorption is maintained by the flow of blood and lymph to the alimentary tract. Concentration of absorbed agent in blood and lymph is maintained at a low level by dilution, protein binding, metabolism and even excretion, e.g., back into other parts of the alimentary tract by bile, or through kidney, lung, or skin. The rate of transfer into the organism is determined by physicochemical properties of agent and membrane, and the concentration gradient.

Membranes of the alimentary tract behave as if they contain sites with special properties designated as carriers. These carrier sites enhance absorption of many molecules whose polar structure would otherwise greatly limit their entry rate. Carriers may act to enhance transport of an agent by facilitated diffusion or active transport. In facilitated diffusion the agent-substrate reacts with the carrier component of the membrane, and transfer between the two faces of the membrane is greatly facilitated without expenditure of cellular energy. The same process occurs identically on both sides of the membrane. Facilitated diffusion shows the following characteristics: (1) movement down a concentration gradient; (2) increased transport rate in the biological as compared with a simple membrane; (3) saturation phenomenon: as luminal concentration is increased, transport increases in proportion until all carrier sites are filled, after which further increases in concentration do not further increase transport rate; (4) no change in substrate during transport; (5) transport system functions in the same way from both directions; (6) competition between structurally analogous substances: when the transport site is utilized by another substrate, it is not available for transport; effects of competition depend on relative affinities of substrates for carriers; (7) countertransport: movement of a substrate with high luminal concentration into the cell may be accompanied by movement out of the cell into the lumen of a similar molecule having a high intracellular concentration.

Active transport is similar to facilitated diffusion except that the agent-substrate can be moved out of the lumen against its concentration gradient. This requires expenditure of energy and can be unidirectional. Active transport can control rate of transport and thereby the internal environment or concentration of specific substances. Hydrolysis of adenosine triphosphate probably provides the energy for most active transport processes.

Pinocytosis is cellular uptake by the process of engulfing particles or dissolved material through formation of a vesicle using the surface membranes of the cell. This is a type of active transport and requires energy. Intestinal cells of newborn mammals have a particular ability to absorb immunoglobulins by pinocytosis. This is the mechanism of passive transfer of maternal immunoglobulins in the milk. Although present at birth, this capacity largely disappears within a short time corresponding to several replacements of intestinal epithelium. This fetal and newborn mechanism persists into adulthood, at least to a minor extent, as shown by pinocytotic vesicles in adult rodents. Absorption of intact macromolecules by adult humans causes allergic phenomena. Such sensitization is probably caused by proteins absorbed by pinocytosis, but macromolecules may also enter through the desquamation zone at the tip of the villus. Particles such as asbestos fibers, which have been shown to penetrate through the digestive tract of rats (*15*), probably enter by this mechanism. A persorption mechanism for entry of macromolecules and solid particles has been described (*16*).

Most environmental agents are absorbed by passive diffusion whereas most nutrients, e.g., sugars, amino acids, vitamins such as thiamin, niacin, riboflavin, pyridoxin, are absorbed by carriers. Environmental agents that are acids or bases also enter the organism by diffusion, but their entry depends on pH in the lumen and at the interface. In general, charged molecules do not enter and penetrate the membrane. Hence, acids and bases enter the membrane only in their un-ionized form, where they have maximal lipid solubility. Thus, most weak acids, e.g., salicylic acid and aspirin, are best absorbed from the stomach.

The acidity of the stomach ensures that the acids are essentially un-ionized and in their lipid-soluble form. The lowest pK_a of an acid compatible with rapid absorption is about 3. In contrast with acids, environmental agents that are weak bases form salts in the stomach and are completely ionized. Thus, when hydrochloride salts of basic drugs (formed by the reaction of gastric hydrochloric acid with drug) enter the small intestine, the pH rises to 5–7 as the acid is neutralized, and the lipid-soluble free base is liberated. The lowest pK_a for a base that permits formation of free base at pH 5–7 is about 7.8. Strong bases retain the salt form, remain ionized, and are not absorbed in the small and large intestine. Similarly, strong acids ($pK_a < 3$) are not protonated in the stomach to form the neutral molecule. Hence, they are not absorbed from the stomach, and remain completely ionized and unabsorbed as they traverse the small and large intestine.

In summary, the intestinal membrane, like cell membranes generally, acts as a lipoid barrier and preferentially allows passage of lipoidal substances. Rate of absorption is related to oil-water partition coefficient of the agent: in general the more lipid soluble, the more rapid the absorption rate. Acids and bases cross the membrane only in their unionized (lipoidal) form. The gastric contents have a low pH in the range of 1–2 and convert acidic agents to their neutral, lipid soluble form. Thus, acids are absorbed from the stomach. Bases are converted to charged lipid-insoluble salts in the stomach, but are reconverted to the free base in the small intestine where they are absorbed.

INTRACELLULAR PROCESSES: ENZYMES, ENZYME INDUCTION, CONJUGATION, METABOLISM: Intestinal mucosa is capable of metabolizing a wide variety of substrates (*5, 17*). Metabolic processes occurring within the mucosal cell are critical in determining results of interactions between environmental agents and the alimentary tract. Absorption rates of such agents must be considered concurrently, since this determines delivery rates of agents into the cells, thereby influencing metabolism. Chemical agents present in the environment that are ingested are analogous to drugs. Total body rates of metabolism of a given drug differ among individuals by factors of 3–10. Based on studies in identical twins, this degree of individual variability can occur simply on a genetic basis (*18*). Individual variability in the metabolism of environmental factors by the alimentary tract has not been defined. Rates of intestinal transport of environmental chemicals might also differ greatly, simply on a genetic basis as discussed in a subsequent section.

Metabolism of drugs and chemicals is also highly dependent on individual factors not genetically determined. Many drugs and chemicals induce hepatic microsomal enzymes. Such enzymes are also induced in the alimentary tract, particularly the small intestine (*19*). Recent work is of particular relevance to effects of environmental factors on the alimentary tract. Environmental chemicals induce enzymes in the alimentary tract that alter their own absorption and that of other agents. Effects of natural foods differ from those of semisynthetic diets, and even the way in which food is prepared has an effect. These studies were carried out by using the rat as experimental model and phenacetin, a common over-the-counter analgesic, as the environmental factor (*20*). Prior studies in the rat had demonstrated an enzyme system that metabolized phenacetin to *N*-acetyl-*p*-aminophenol in the wall of the small intestine (probably the mucosal epithelial cells). Activity of this enzyme system is increased in rats pretreated with environmental factors such as cigarette smoke, with 3,4-benzpyrene, a constituent of cigarette smoke, or with 3-methylcholanthrene. This increased metabolism by the intestine probably decreases the amount of phenacetin absorbed unchanged into the bloodstream. These findings explain the observation that cigarette smoking in man enhances metabolism and lowers plasma concentration of orally administered phenacetin without changing plasma half-life. The current study showed that even commercial rat chow (the equivalent of natural food) has components promoting metabolism of phenacetin by intestine *in vitro*. Purina rat chow was compared with a nutritionally complete semisynthetic diet (normal protein test diet containing vitamin-free casein, 27%; starch, 59%; with vegetable oil, 10%, and salt and vitamin mixes). The small intestine from animals taking the semisynthetic diet formed *N*-acetyl-*p*-aminophenol at one-third the rate of those ingesting the commercial chow. Thus, even components in natural diets alter metabolic activity of the intestine. In addition, when charcoal-broiled ground beef was added to the semisynthetic diet, rate of phenacetin metabolism by intestine increased elevenfold. In comparison, addition of raw ground beef or ground beef cooked on aluminum foil to the semisynthetic diet changed metabolism of phenacetin only minimally. These results suggest that normal diets of natural food or differences in the means for cooking food alter intestinal metabolism of environmental factors, and thereby could decrease their absorption and effects on the organism. Ingestion of charcoal-broiled beef also alters phenacetin metabolism in man (*21*).

Another study has also demonstrated that behavior of intestinal mucosal drug metabolizing enzymes is different from that of liver in being more directly dependent on diet. A high-cholesterol diet enhances mucosal activities of several enzymes including aryl hydrocarbon hydroxylase. Polychlorinated biphenyl decreases mucosal enzyme activities of such animals in contrast to stimulation of hepatic enzymes (*22*). In duodenal mucosa lipid diets decrease activities of drug hydroxylation and glucuronidation (*23*). Metabolism of hexobarbital, phenacetin, 7-ethoxycoumarin, and benzo[a]pyrene by duodenum and proximal jejunum *in vitro* is increased in rats fed dried Brussels sprouts or cabbage added to a complete semisynthetic diet as compared to rats fed only the semisynthetic diet (*24*). Pretreatment of rats with indoles present in Brussels sprouts and cabbage also stimulated intestinal drug metabolism. Indole suppresses hepatotoxicity of 2-acetylaminofluorene (*25*). Nutritional factors also influence oxidative metabolism of antipyrine and theophylline in man (*26*). Increasing dietary carbohydrate prolongs drug half-lives, whereas protein supplements decrease drug half-lives.

Toxic effects of cadmium include those on the alimentary tract such as depression of absorption of diverse nutrients including calcium, phosphorus, copper, glucose and alanine. Cadmium appears to be unique among toxicants in inducing synthesis of a protective factor in the gut (*27*). Incorporation of cystine into the protein fraction containing thionein, a cadmium-binding protein, is increased by feeding cadmium. Total protein synthesis is also increased in intestine of cadmium-fed animals as shown by intestinal weight and protein.

Effects Related to the Environmental Factor

Environmental agents that enter the alimentary tract in solution are available for absorption by processes discussed above. Those agents that are not dissolved must enter solution prior to absorption.

Rate of dissolution is determined by thermodynamic properties of the system, size of particles and hence their total surface area, and properties of the surface of the particle. Agents may have slow dissolution rates and this may be the limiting step in the absorption process. Factors affecting dissolution rate of slowly soluble substances are surface area of dissolving solid, crystal form of the agent and its state of hydration, and solubility in the diffusion layer. The greater the surface area of the agent in contact with the solvent, i.e., the intraluminal milieu, the more rapid the rate of dissolution. Therefore, the smaller the size of particles, the more rapid the dissolution rate. Solubility of the agent in the diffusion layer of high concentration immediately surrounding the particle of agent is important in determining rate of solution of a particulate agent. Solubility of a particle of acid, e.g., aspirin, can be increased by raising the pH as happens when the particle passes from stomach into small intestine. Similarly, solubility of a base can be increased greatly by presence of gastric acid which forms the highly water soluble salt of free base in the medium immediately surrounding the particle. Agents may be polymorphic, i.e., exist in more than one crystalline form. Differences in physical properties of polymorphic forms include differences in solubility and dissolution rates. Some agents may exist in either crystalline or amorphous forms. Amorphous forms are always more soluble. If an environmental agent exists in more than one state of hydration, these forms will differ in physical properties, particularly solubility. Usually the anhydrous form is more soluble than the hydrate.

Rate of solution also depends on behavior of the medium. As a solid particle dissolves, a saturated solution forms around the surface of the particle in the immediately surrounding liquid. This decreases rate of dissolution of the particle. Hence, the normal motility of the alimentary tract which mixes its contents and moves the saturated solution away from the particle enhances absorption. After molecules of the agent have dissolved, they must diffuse from the high concentration zone around the particle through the contents of the lumen to the membrane barrier. Motility aids in this distribution.

Thus, the effective or toxic dose of an agent is determined by many factors in addition to the total dose entering the organism. The toxic form is usually that in solution as it enters or dissolving after entry. This fraction of the dose may be altered intraluminally, trapped in the mucosal cell, metabolized by the cell, or transferred into the organism, i.e., absorbed. The proportion of agent following the various pathways depends on the total dose and pattern of entry into the organism, as well as physical form of the agent. After it enters, effects of the agent depend on individual factors such as age, sex, disease of the subject, and presence of adjuvants altering availability of agent to the organism. Hence, effective dose depends on factors related to the agent and to the individual.

Effects Related to the Individual: Modifying Factors

Disease or injury to the alimentary tract occurs within the setting of the person at risk. This individual is defined in terms of age, sex, general health, nutrition, status of induction of hepatic smooth endoplasmic reticulum, usage of drugs (Tylenol, Valium, aspirin), ethanol, tobacco.

Age: Effects of age on responses of the alimentary tract to environmental agents have yet to be defined. The alimentary tract of the young animal is about 5% of total body weight. Subsequently, the animal grows in body weight more rapidly than in weight of alimentary tract, and the proportion of weight of alimentary tract to body weight declines to about 2.5%. A constant relation between body weight and alimentary tract weight is then established. Toxic agents would be expected to have their greatest effect during rapid growth. The continuous renewal of epithelium of the alimentary tract throughout life also increases its vulnerability to toxic agents.

Gastric acidity enhances absorption of acids, but depresses absorption of bases moving absorption site distal to the stomach. In newborns gastric acidity approximates that of adults for the first 24 to 48 hr of life. After 48 hr, acidity declines (pH increases) steadily to a minimum level of acid at 10 days. Gastric acidity then increases (pH decreases) until the third year of life, when adult levels are approached. In the adult, gastric acidity decreases with aging, and low gastric acidity (high pH) is common in the elderly. Thus, rate and site of absorption of acids and bases varies with age.

Genetic factors: Hereditary defects of the small intestine alter intestinal homeostasis and thereby influences effects of environmental agents. Most genetic defects lead to diarrhea and depressed absorption of normal nutrients. This diarrhea is undoubtedly also associated with depressed absorption of toxins.

Membrane Transport Defects: Glucose-galactose malabsorption, disaccharidase deficiency, congenital chloridorrhea are examples of genetic transport defects producing osmotic diarrhea. The increased intraluminal volume and rapid transit alters luminal distribution as well as absorption of toxins.

Membrane Digestive Defects: Digestive enzyme deficiencies of the mucosal brush border such as disaccharidase deficiencies (e.g., lactase, sucrase-isomaltase) also cause osmotic diarrhea.

In the newborn, during the suckling period, and in childhood, high levels of lactase are normally present in the small intestinal mucosa. In most of the world's population, lactase levels decline before adolescence and lactase deficiency is the norm for adults. Only northern Europeans, their emigrant populations to other parts of the world, and certain other ethnic groups with a dairying technology have levels of intestinal lactase in adults adequate for rapid digestion of dairy products such as milk and ice cream. Thus, most adults experience abdominal discomfort from increased motility due to osmotic diarrhea after lactose ingestion and tend to avoid milk products. The physical dimensions of the luminal milieu in patients with lactase deficiency is shown in Fig. 2. Those lactose-intolerant individuals who chronically ingest lactose would be expected to show altered absorption of environmental factors of a chemical nature. Postweanling young rats, like man, develop intestinal lactase deficiency. Studies in this animal model have provided data relevant to effects of lactase deficiency on environmental toxins (*28*). Rats fed 10 or 30% lactose were compared with populations fed equivalent amounts of sucrose. These carbohydrates were substituted in the basal diet. Fecal fat and nitrogen were significantly greater in the lactose fed group,

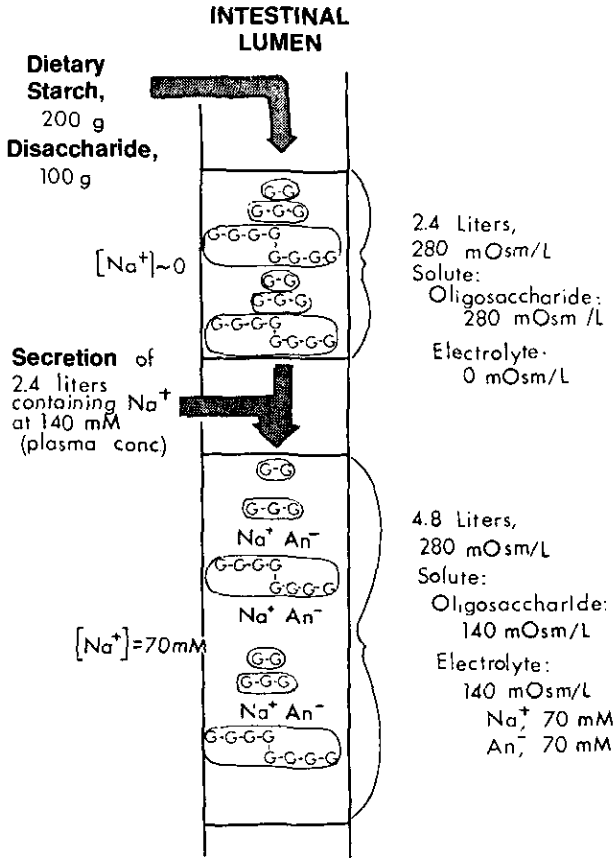


FIGURE 2. The daily intake of carbohydrate yields 662 mOsm of unabsorbable solute, if pancreatic function is adequate but mucosal disaccharidase activity is lacking. Assuming this osmotic load arrives in the jejunum unaccompanied by other solutes, its volume would be 2.4 liters, because of permeability of the intestinal mucosa to water. The luminal sodium concentration in equilibrium with plasma is 120 to 127*mM*. Since intraluminal sodium concentration is assumed to be zero, the steep blood-to-lumen gradient of sodium concentration results in sodium secretion. Dilution of luminal contents with an equal volume of secretions containing sodium at a concentration equal to that of plasma raises luminal sodium to 70*mM*. Since luminal sodium concentration is still low relative to the gradient of concentration established by the small intestine, more sodium is secreted. An additional 2.4 liters of secretion raises luminal sodium to 93*mM*. From Schedl (*6*). Reproduced through the courtesy of the W. B. Saunders Co., Philadelphia, Pa.

although increases were small, i.e., of the order of 2%. Fecal calcium excretion was lower in the lactose fed group, and the decrease was significant in the group fed 30% lactose, despite more rapid transit of intestinal contents in the lactose-fed group.

The effect of the diarrheal state to increase fecal fat and nitrogen excretion is predictable and the same finding would be expected with environmental agents having physical and chemical properties similar to the precursor lipids and proteins. Effects on calcium excretion are unexpected and might be due to enhancement of calcium absorption by lactose, greater than the depressant effect of rapid transit. Similar effects might be observed with other cations present as environmental toxins such as strontium, cadmium, lead, or even iron.

Diseases of the Alimentary Tract: Gastric acidity is decreased in chronic gastritis, after gastric surgery, with reflux of intestinal contents into the stomach, and in pernicious anemia. All of these conditions alter absorption of strong acids and bases by the stomach and proximal small intestine.

Systemic Disease: Diseases altering intestinal function will change effects of environmental agents on the organism. Examples are thyrotoxicosis and other diseases increasing intestinal motility.

Specific Injury or Disease Process: Carcinogenesis

Since cancer of the alimentary tract is by far the most important effect of environmental agents, general aspects will be treated in this section. Cancer of specific organs of the alimentary tract will be considered separately in a subsequent section. The overall magnitude of the problem is illustrated by data presented in Cancer Statistics, 1976 (*29*). Considering cancer incidence by site and sex, cancer of the oral cavity comprises 2% of all cancer in women and 5% of cancer in men. Cancer of colon and rectum comprises 14–15% of all cancer, and other digestive organs associated with the alimentary tract comprise 9–12% of cancers. Cancer deaths by site correlate closely with incidence. Estimates of new cancers for 1976 by site gives added perspective to the scope of the problem: with the total number of new cases of cancer estimated at 675,000, the following estimates were made for the alimentary tract: oral cavity, 23,800; esophagus, 7,500; stomach, 22,900; small intestine, 2,200; colon, 69,000; rectum, 30,000. Estimated cancer deaths for 1976 parallel the pattern of new cases. For a total of 370,000 cancer deaths, estimates for the alimentary tract were as follows: oral cavity, 8,300; esophagus, 6,600; stomach, 14,400; small intestine, 700; colon, 38,900; rectum, 10,300.

Alimentary tract cancers from action of environmental factors are examples of chemical carcinogenesis. A recent critical review of this topic (*30*) illustrates general principles applicable to the alimentary tract, including possible model systems for evaluation of carcinogenesis. Metabolic activation to carcinogens as well as inactivation of carcinogens occurs in the alimentary tract. *N*-Nitroso compounds (nitrosamines) are among the most important environmental carcinogens, and progress in this field has recently been reviewed in proceedings of a working conference (*31*). Recent experience on exposure to *N*-nitroso compounds in the United States has been reviewed (*32, 33*). In addition to entering the body through the alimentary tract, nitrosamines can form in the human digestive system: nitrite in saliva formed by reduction of nitrate by normal oral microflora is swallowed and in the stomach is converted to nitrous acid which reacts with amines. Potentially carcinogenic nitroso compounds are also readily formed in the stomach from drugs with secondary alkylamino structures (e.g., nortriptyline and fenfluramine) on the basis of studies with human gastric juice under simulated gastric conditions (*34*).

On the basis of epidemiologic evidence, it is estimated that 80–90% of all human cancer may be related to one or more environmental factors. Since most of these factors probably enter the organism via the alimentary tract, effects related to the gastrointestinal system may be critical to carcinogenesis. It is of particular importance to understand this interaction because most of this disease is potentially preventable. Dietary nutrient factors, probably acting through alimentary tract mechanisms, influence the development of neoplasms. The role of dietary constituents in altering responses to carcinogens has recently been reviewed (*35*). In both human and animal studies dietary fat intake increases incidence of carcinomas. Mechanisms of such effects are not known but may include increasing absorption or altering distribution of carcinogens, possibly by changing bile salt metabolism. Gastrointestinal microflora has been postulated to have a role in carcinogenesis: bacteria, particularly clostridia, may metabolize bile acids to produce unsaturated compounds that act as carcinogens or cocarcinogens. The composition of the diet interacting with functional activity of various organs of the alimentary tract has a major role in determining the type of enteric bacterial flora and fecal bile acid concentration and hence amount of carcinogen produced.

Clostridia and Bacteroides species can also carry out reactions that reverse the metabolic activation of a carcinogen. Thus, 4-acetylaminobiphenyl is metabolically activated to a carcinogen by conversion to *N*-hydroxy-4-acetylaminobiphenyl. Enteric organisms can reduce the carcinogen to the parent compound, hence influencing levels of metabolites of 4-acetylaminobiphenyl which may be critical for carcinogenesis (*36*). Certain biologically active epoxides are carcinogens. Since microbial organisms found in the digestive tract of ruminants reduce the epoxide group, such reductions may be important in detoxication of carcinogenic epoxides (*37*).

The nutritional state of the organism is dependent on function of the alimentary tract. Emphasizing the role of the alimentary tract in cancer, it is estimated that half of female cancers in the Western world and one-third of all male cancers are related to nutritional factors (*38*). Carcinogens also occur naturally in foods (*39*). Environmental factors such as vitamins acting by alimentary tract mechanisms may be very important in development of cancer (*40*). Thus, vitamin A is essential for maintenance of glycopeptide in the epithelium of the gastrointestinal tract. Reduction of tissue levels of vitamin A slightly below normal values, such as might occur in malabsorptive diseases, results in greatly reduced synthesis or disappearance of glycopeptide from the epithelium. The precise role of this vitamin A-dependent component of epithelium remains to be determined, but it appears to be associated with maintenance of epithelial integrity, possibly through its influence on cellular differentiation. Integrity of the epithelium may be important in determining absorption of ingested agents. Decreased dietary and tissue levels of vitamin A are associated with carcinoma of the colon in rats, and higher than normal vitamin A intake protects hamsters from benzo[a]pyrene-induced lung cancer. Retinoids have some ability to prevent chemical carcinogenesis in epithelial tissues of bronchi, trachea, stomach, uterus and skin in animals (*41*).

Partial List of Environmental Diseases of the Alimentary Tract Classified by Specific Organs

Mouth

Diseases of the mouth include periodontal disease, caries, and fluorosis.

Esophagus

Esophagitis: Acute esophagitis may be caused by corrosive agents, either acids or alkalis.

Drug-induced chronic esophagitus may be directly caused by drugs or may be secondary to drug-induced inhibition of the lower esophageal sphincter with resulting acid reflux.

Cancer: Environmental factors probably play a key role in genesis of esophageal cancer as evidenced by the enormous difference in incidence in different geographical locations. The highest recorded rates occur in southern Africa and the area near the Caspian Sea (*42*). Of interest is the finding that incidence of esophageal cancer in Brittany is several times that observed in the United States (*43*). Since the male to female ratio is 24:1, environmental causes are almost certainly operative.

Stomach

Gastric and duodenal (peptic) ulcers may result from environmental stress or may be induced by drugs such as aspirin (*44*) or indomethicin.

Acute gastritis may be due to alcohol or smoking.

Chronic gastritis of unknown etiology is a prevalent disease. Its importance lies both in direct effects and in its possible relationship to gastric cancer. Long-term chronic gastritis may provide the setting for development of gastric cancer. Many agents probably contribute to development of gastritis. In our society chronic gastritis is caused by artificial agents such as drugs and possibly by environmental pollutants, especially those in water and food. In primitive societies, chronic gastritis may be the result of components of the food and drink of the natural environment of inhabitants.

Because of its prevalence and possible relation to gastric cancer, specific avenues of research related to chronic gastritis should be identified. More information on incidence and prevalence should be accumulated.

Overall death rates from stomach cancer have been declining in the United States and have begun to decline in Japan.

Small Intestine

Sprues: Nontropical (celiac) sprue is a rare disease caused by peptides in the gliadin fraction of wheat gluten.

Tropical sprue is a chronic disease prevalent throughout the world in underdeveloped countries. It occurs in natives of developed countries after living in endemic areas and remits on return to developed country. It causes impairment of absorption of nearly all nutrients: inefficient utilization of nutrients in the diet causes generalized nutritional deficiency. Inhabitants of underdeveloped countries eat a marginal diet, and any interference with absorption magnifies the effect of marginal intake. The disease has a multi-factorial etiology, sometimes occurring in epidemics in a form different from the endemic form. It is a self-perpetuating disease, since the poor nutrition caused by the disease itself causes the malabsorption to worsen by damaging structure and altering function of the alimentary tract.

This is a widespread disease of tremendous impact on world health. Its cause is unknown and multiple environmental factors undoubtedly contribute. Potentially fruitful lines of attack on this problem should be identified.

Regional Enteritis (Crohn's Disease): This is a disease of distal small intestine but may involve any site in the alimentary tract. It is particularly likely to involve the colon adjacent to the ileum. Environmental agents are probably important in this disease of Western civilization which is rare or absent in underdeveloped countries. Fruitful lines of investigation should be identified and pursued.

Other diseases of the small intestine include drug-induced villus atrophy (neomycin, antimitotic agents) and alteration of the bacterial ecosystem. Cancer of the small intestine is rare in comparison with other sites.

Colon

Colitis: Diseases of consequence are ulcerative colitis, Crohn's colitis, and necrotizing enterocolitis. The last entity includes pseudomembranous enterocolitis, a condition that is increasing in incidence and recognition and is directly related to use of antibiotics, particularly lincomycin and clindamycin, by both oral and parenteral administration. Interactions between changes in bacterial ecosystem, unknown factors, and the host organism produce the disease. Now widely prevalent, this disease may provide the clue to understanding the pathogenesis of the inflammatory bowel diseases, regional enteritis and ulcerative colitis. These are diseases of developed countries, continually increasing in incidence and prevalence, and environmental factors are probably critical in their pathogenesis. Pseudomembranous enterocolitis is readily diagnosed by sigmoidoscopy, and the extent of the disease can be determined radiographically.

Its incidence should be determined by developing a routine for population surveillance, including double-blind studies of people treated with antibiotics and those not treated. Animal models should be developed for examining the disease. Determining effects of the antibiotics that cause the disease on bacterial populations and on the function of the involved organs is also a goal. Synthesis of DNA, cell division, and metabolism of mucosal epithelium should be studied.

Other diseases of the colon are diverticular disease and irritable (spastic) colon, which is a functional response to environmental stress.

Cancer: Epidemiology of colonic cancer has been reviewed extensively (*45, 46*). The major hypothesis to be tested relates to the interaction of the alimentary tract with environmental factors: diet determines intraluminal components of endogenous origin (e.g. bile acids, neutral steroids, digestive enzymes, etc.) and composition of enteric microflora thereby determining production of carcinogens and cocarcinogens from intraluminal compounds. Environmental factors may be critical contributors to these processes.

Environmental Agents Related to Alimentary Tract Disease

Excellent background documents are already available for two major categories of agents of great importance to the alimentary tract: toxicants occurring naturally in foods; and food additives and chemical residues in food.

A comprehensive treatment of toxicants present even in the normal diet was published in 1973 (*47*). Entry and possible initial impact of all such toxicants is in the gastrointestinal tract. The following examples are typical of problems encountered and factors to consider.

Nitrates and nitrites are examples of anions of acids that are rapidly absorbed directly from the stomach. The high excretion rate of nitrate in urine appears to account for lack of toxicity of nitrates and nitrites under normal conditions of exposure. Chronic feeding studies in rats and dogs show no remarkable effects of nitrates or nitrites on the alimentary tract.

The toxicity of ingested kidney beans has been postulated to result from interaction of their hemagglutinins with cells lining the gut. Adsorption of bean agglutinins onto the surface of mucosal cells has been shown by *in vitro* experiments on rat intestine. Resistance of hemagglutinins to digestion is readily demonstrated by the hemagglutinating activity of extracts from feces of rats ingesting a raw bean diet. Fecal nitrogen is increased in rats fed a raw bean diet, suggesting decreased intestinal absorption or increased loss or protein from the alimentary tract. In animals previously given black bean agglutinin by stomach tube, glucose absorption from a ligated intestinal loop is low compared to controls animals. Rats fed a bean diet experience severe hypoglycemia, which may be caused in part by poor absorption of glucose. Raw beans interfere with amino acid absorption and utilization of vitamin E in chicks. Raw soybeans may also interfere with absorption of various nutrients.

Corrosive gastroenteritis follows ingestion of oxalic acid. Since oxalic acid probably does not exist in the free form in plants, and oxalates in spinach and rhubarb are principally as calcium or potassium salts, the role of oxalic acid in toxicity of these plants has not been established. No typical gastrointestinal tract lesion has been identified in children who died after eating rhubarb leaves and stalks.

Brown mustard contains allyl isothiocyanate, a potent irritant of the gastrointestinal tract. This compound is also found in broccoli and cabbage. Allyl isothiocyanate produces epithelial hyperplasia and ulcers of the stomach when fed to dogs, but has no effects in the rat and it is unlikely that toxic doses are ingested by humans.

The background document (48) prepared for the First Task Force on Research Planning in Environmental Health Science covers evaluation, including toxicology and testing, of food additives and chemical residues in food, and outlines research needs.

Recommendations

As outlined in this report, the gastrointestinal tract is the major portal of entry and a primary site of injury for environmental factors. To cope with these problems, they must be more fully defined and their mechanisms determined by basic and applied research so that management and treatment can be instituted. Thus, the major needs are trained personnel and research and are the basis for the following recommendations.

RECOMMENDATION 1: It is essential to provide personnel with appropriate training and orientation for research, clinical evaluation, and treatment (individual or environmental) of problems caused by environmental agents.

These individuals are biochemists, physiologists, pharmacologists, microbiologists, and other basic scientists oriented toward the gastrointestinal tract by their interests and training. In addition, personnel trained in gastroenterology as well as other clinical disciplines related to the alimentary tract such as pathology are needed for clinical application of basic research findings, as well as for identifying problems and their management. This also requires research on the problems in collaboration with basic scientists. This team of basic and applied scientists would interact with scientists primarily oriented toward environmental health sciences in seeking solutions to important problems. The complex nature of problems posed by interaction of the organism with environmental factors via the gastrointestinal tract, as outlined in this report, makes a team approach imperative.

RECOMMENDATION 2: Although the gastrointestinal tract is the major interface between organism and environment and modulates this interaction, basic information is lacking. The role of the gastrointestinal tract in this modulation should be defined and mechanisms producing these effects should be determined.

As defined by this report, modulation is specific and characteristic for each organ and interaction with the agent occurs during its passage longitudinally through the alimentary tract. Modulation also occurs as the agent moves centrifugally from lumen into tissue at the following physical and anatomic loci: lumen, brush border, within the mucosal cell, at the basal-lateral cell membrane, within the lamina propria, submucosa, vascular and lymphatic systems of the gastrointestinal tract. Specific studies at each locus as well as overall effects require examination. It is recommended that the following important problems outlined in this report be studied.

RECOMMENDATION 3: Basic research on the intraluminal milieu of the gastro-intestinal tract, particularly as a bacterial ecosystem and biochemical environment is essential.

The role of the normal bacterial ecosystem should be defined and in this setting effects of abnormalities of the ecosystem should be examined for potentiation or protection from actions of environmental factors. Populations with the following conditions should be examined: postgastrectomy, blind loops, strictures, diverticula, diabetic gastroenteropathy, etc. The chemical intraluminal milieu and its effects on environmental agents in the normal person and in disease should be examined with respect to role of specific secretions at each site in the alimentary tract: pH, digestive enzymes, detergent effects from bile salts, interaction with mucus, etc. Patients with abnormalities of luminal contents should be examined for differences from normal in handling environmental agents and differences in incidence of disease. Conditions such as achlorhydria, pancreatic and biliary insufficiency etc. should be studied.

RECOMMENDATION 4: The role of the brush border in modulating effects of environmental factors in normal and disease states should be examined. Properties of the brush border promote or inhibit absorption, and its enzymes cause chemical reactions such as digestion. Brush border diseases that alter interactions with environmental factors include brush border enzyme deficiency in celiac sprue and tropical sprue, loss of brush border surface by small intestinal resection for inflammatory bowel disease or bypass of the small intestine for treatment of obesity.

RECOMMENDATION 5: The role of intracellular processes within cells lining the gastrointestinal tract in modulating effects of environmental agents should be determined for normal and disease states.

Transformations within the mucosal cell include digestive and hydrolytic processes, synthetic reactions such as conjugation and esterification, and degradative processes such as oxidation. These processes should be evaluated in relation to environmental factors. Enzyme induction by one environmental agent may alter disposition of another. Effects of disease of mucosal cells (see Recommendation 4 above) on intracellular disposition of environmental factors and incidence of environmental disease should be examined.

RECOMMENDATION 6: Cancer of the alimentary tract and other organs is the most important disease caused by environmental agents. The alimentary tract is the main portal of entry for carcinogens and the role of the alimentary tract is inhibiting and promoting development of cancer in the tract and elsewhere should be determined.

RECOMMENDATION 7: Diseases known to be caused by environmental agents such as cancer of esophagus, stomach and colon should be monitored for changes in pattern or incidence.

RECOMMENDATION 8: Continuous prospective observations for development of new diseases of the alimentary tract caused by environmental agents are necessary.

RECOMMENDATION 9: Important naturally occurring environmental diseases such as celiac and tropical sprue should be investigated to determine etiologic and biochemical mechanisms of disease. Certain specific diseases induced by artificial agents such as pseudomembranous enterocolitis should be studied as model systems that may provide basic understanding.

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